REMARKS/ARGUMENTS

In the Claims

No new matter is believed to be added by this Amendment. Claims 59, 96 and 107 are amended herein, to accommodate the Examiner's concern that various acronyms such as IL-4 have not been defined upon the first use in the claims (page 5 of pending Action; top). Support for the amendments may be found throughout the application, including for instance at page 25 line 13 to page 26 line 11 and page 33 lines 21-23 of the application as filed.

Response to new rejections under 35 U.S.C. §112:

1. Claim 55

   In the present Action, pending claim 55 is rejected as indefinite, with the rejection stating it is not clear how two substances can be one substance, even in two forms.

   In response, Applicant respectfully points out page 14 lines 21-25 of the application as filed, which states that "two forms of a substance" means two ionization states or salt forms of the same substance, two different complexes of such substance, and so forth. With regard to the construction of the claim, reference to "a substance" in claim 55 should be clear as other references to substance(s) in claim 54 are concerned with "at least two substances". In response to the question, Are there 2 substances or 2 forms of 1 substance, Applicant respectfully submits that there are 2 substances (as in claim 54).

   In the event that the Examiner maintains this rejection, to further prosecution of this application, Applicant agrees to cancel claim 55.

2. Claim 61

   In the present Action, pending claim 61 is rejected as indefinite, with the rejection stating it is not clear what is meant by "associated with the penetrant".

   In response, Applicant respectfully points out page 26 lines 16-22 of the application as filed, which states that "associated with the penetrant" means for example in the form of a complex, hetero-aggregate, via encapsulation etc. Applicant notes that for instance different active ingredients may have different chemical properties and may undergo different interactions with penetrants of the present invention. Depending on an active ingredient's chemical properties, an active ingredient may for instance be contained within the penetrant and/or attached in some way to the interior or exterior of the penetrant.

   In the event that the Examiner maintains this rejection, to further prosecution of this application, Applicant agrees to cancel claim 61.

3. Claims 93, 102, 105

In the present Action, pending claims 93, 102, 105 are rejected as indefinite, with the rejection stating it is not clear what the term "derived from" and "derivative" is intended to mean.

In response, Applicant respectfully submits that the term "derived from" a pathogen means originating from a pathogen, and that a "derivative" of a peptide means a peptide that has been chemically altered possibly so that it is no longer a true peptide. Also, Applicant respectfully points out page 32 lines 11-20, noting that "derivatives" of an antibody or immunoglobulin include chemical, biochemical and otherwise obtainable derivatives, such as genetically engineered antibody derivatives.

In the event that the Examiner maintains this rejection, to further prosecution of this application, Applicant agrees to cancel claims 93, 102, 105.

4. Claims 59, 96, 107

In the present Action, pending claims 59, 96, 107 are rejected as indefinite, with the rejection indicating various acronyms should be spelled out in the claims.

In response, Applicant submits claims 59, 96, 107 have been amended to spell out acronyms.

In the event that the Examiner maintains this rejection, to further prosecution of this application, Applicant agrees to cancel claims 59, 96, 107.

Response to new rejections under 35 U.S.C. §103:

In the present Action, claims 54-59, 61-63, 65-87, 89-93, 97-103 and 105-114 are rejected under 35 U.S.C. 103(a) as obvious over Cevc (Biochem. Biophys. Acta., Jan 19, 1998, Vol. 1368(2):201-215) and Modi (US 5,653,987). Specifically, the Action states that Cevc discloses a transdermal pharmaceutical preparation having insulin, soybean phosphatidylcholine and sodium cholate that meets the structural/composition limitations recited in claims 54 and 100 of the present application, and that Modi discloses formulations for nasal drug delivery having an active ingredient and at least two absorption enhancing compounds which can include sodium deoxycholate or Tween 80 and phospholipids(phosphatidylcholine and phosphatidylethanolamine). The Action also states that the skilled person would be motivated to practice the present invention in view of these two documents because Cevc teaches the formulations of the present invention and Modi teaches phosphatidylcholine and sodium deoxycholate are useful for enhancing nasal administration of various substances. Claims 60, 88 and 94-96 are also rejected as obvious over the combination of Cevc and Modi, in combination with other documents.

In response, Applicant submits that the present invention is not obvious in view of Cevc and Modi, for at least the reasons discussed below.

Cevc discloses the preparation of a special composite body, a transfersome, that can deliver insulin across pores in the skin, even through pores appreciably smaller than the transfersomes. (See e.g. page 202 first full paragraph). Cevc expressly states that such delivery is dependent both on the transfersome's deformability and the transepidermal water gradient of the skin. See for instance the

top of page 205, right column lines 1-4, where Cevc discloses that when a vesicle having a radius r_v is pushed into a confining pore having a radius that is less than or equal to r_v, work must be done to pay for activation energy of the process, so the vesicle may enter the pore. Cevc further discloses that this energy is proportional to the vesicle's size (surface area) and the deformability of the vesicle's membrane (page 205 right column lines 4-11). Cevc performed studies to determine how this energy requirement was met, and found that the transepidermal water activity gradient drives transfersomes into and across the skin. (page 204, bottom right column). According to Cevc's research, transfersomes spontaneously transported insulin across the epidermal horny layer both because the transfersomes were deformable enough to enter and squeeze through pores, and because the epidermal horny layer of the skin provides a gradient that provides energy sufficient to allow the transfersome (and associated insulin) to be sucked through the "tortuous space between the horny-cells" and enter the body. (See also Cevc page 205, left column, and page 208, left column 4th full paragraph through right column). Cevc also teaches that high membrane deformability and good sensitivity to transepidermal osmotic stress maximize the speed of transfersome penetration through the skin, allowing delivery of epicutaneously administered transfersomal insulin. (page 208, third full paragraph). Overall, Cevc teaches that transfersomes spontaneously transport insulin across the epidermal layer (page 208 2d full paragraph), due to the deformability of transfersome membranes and the transepidermal water gradient driving the transfersomes through the epidermal horny layer.

Cevc also states that bile salts in its transfersomes do not affect the skin barrier in the same manner as bile salts act in other (non-transfersomal) pharmaceutical preparations: by partly fluidizing the skin and thus effecting entry of insulin (page 212 right column 2nd full paragraph through page 213 line 8). Cevc states that if bile salts in Cevc's transfersomes were acting in such a conventional manner, the measured decrease in blood glucose concentration would increase with increasing bile salt concentration. However, Cevc discloses that such was not observed in their study, and that insulin delivery was mediated by transfersome activity and not by bile salt-induced skin-fluidization or skin lesions.

Modi primarly discloses liquid formulations having at least two "absorption enhancing" compounds that allow for the delivery of insulin through the stomach, despite the stomach's mechanisms for breaking down insulin. In all Examples, Modi discloses administering formulations after pre-treatment of the stomach with a 1 ml solution of salt and sodium bicarbonate to neutralize stomach acid. (Column 5 lines 14-21; Examples I-V). Applicant notes that the stomach is typically a very moist environment; stomachs in all of Modi's experiments contained several milliliters of fluid during insulin delivery, both from the 1 ml pre-treatment volume and the volume of liquid insulin formulation added to the stomach thereafter.

While Modi does not provide any Examples showing nasal insulin delivery, Modi does disclose that its formulations may be used for nasal delivery, as pointed out in the present Action. At column 1 lines 44-52, Modi discloses that nasal delivery of therapeutic agents may be complicated for instance because dosing is variable from one application to the next for instance in view of dripping as a result of irritation of the nasal lining.

1. The skilled person would be taught away from combining Cevc and Modi, at least because Cevc teaches the need for a transepidermal delivery gradient for transfersome-mediated insulin delivery, while Modi teaches applying its compositions on moist (stomach, nasal) tissues devoid of such a gradient.

Taken together as a whole, Applicant respectfully submits that the skilled person would not find the present invention obvious in view of Cevc and Modi. Rather, these documents clearly teach away from the present invention. The skilled person, reading Cevc, would be taught that the transepidermal water gradient created by the epidermal horny layer of the skin provides energy necessary to drive transfersome delivery of insulin through the epidermis and into the body. The epidermal layer includes layer after layer of dead keratinocytes, sealing moisture into the body and providing a dry surface outside of the body, creating a difference in water concentration across the skin. As mentioned in the response and Declaration (particularly paragraphs 7-9) filed about July 2, 2007 in this application, the skilled person would not expect transfersome-mediated insulin delivery across the transnasal barrier, where the transepidermal gradient does not exist. Furthermore, the skilled person would be taught by Modi that Modi's compositions work on moist surfaces including nasal mucosa (recalling Modi's mention of nasal dripping and sneezing) and the lining of the stomach, which in all Examples was well-hydrated by both the liquid insulin preparation and the 1 ml pre-treatment with a liquid having salt/bicarbonate. The skilled person would understand that the transepidermal gradient taught by Cevc does not exist in either the stomach or the nasal mucosa, and therefore be taught that Cevc's transfersomes would likely not deliver insulin through these tissues because of the lack of driving force to push the transfersomes through virtual pores. Applicant notes the skilled person would consider other anatomical differences between the skin and the nasal mucosa/stomach lining as well; for instance, the presence of a thick, moist coat of mucus in the nose/stomach which is not present on the skin.

Overall, the skilled person would be taught by Cevc to use transfersomes on the skin, where there is a dry surface and transepidermal gradient, and to use Modi's (non-transfersome) formulations on moist (oral, nasal) tissue. The skilled person would be taught away from using Cevc's gradient-dependent transfersomes in Modi's moist environments.

At least for the foregoing reasons, Applicant respectfully submits that the present invention is not obvious in view of Cevc and Modi, and requests that the present rejections relating to Cevc and Modi all be withdrawn.

2. The skilled person would not be motivated to combine Cevc and Modi, but rather would be taught away, in view of Modi's teaching of phosphatidylcholine and sodium deoxycholate as enhancing transnasal delivery, at least because Cevc expressly teaches that bile salts used in its transfersomes do not provide the same properties as bile salts known in the art.

In the present Action, the rejection states that, regardless of the mechanism by which the formulation functions (penetration vs. absorption/permeation), a person of ordinary skill in the art would be motivated to practice methods of transnasal administration using Cevc's formulation because Modi teaches that formulations comprising phosphatidylcholine and sodium deoxycholate are suitable for nasal administration.

In response, Applicant respectfully submits that Modi teaches compositions using bile salts as absorption enhancers, and Cevc teaches bile salts as part of a penetrant. As mentioned above, Cevc expressly states that bile salts in Cevc's transfersomes do not provide the same absorption enhancing properties as known in the art, but rather function differently from bile salt compositions in the art. See for instance page 212 right column 2nd full paragraph through page 213 line 8, disclosing that

transfersome-mediated insulin delivery was not caused for instance via bile salt-induced membrane fluidization or creating skin lesions. The skilled person, reading Cevc's express statement that bile salts incorporated into transfersomes do not provide the same effects as bile salts in other preparations, would not be motivated to combine Cevc with Modi therefore.

At least for the foregoing reasons, Applicant respectfully submits that the present invention is not obvious in view of Cevc and Modi, and requests that the present rejections relating to Cevc and Modi all be withdrawn.

Applicant respectfully notes that all pending claim rejections under 35 USC 103 are based on the above combination of Cevc and Modi, and requests that all such rejections be withdrawn therefore.

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Applicant respectfully submits that the present Amendment is fully responsive to the pending Action and places the present application in condition for allowance. Applicant respectfully submits that all pending rejections are overcome and requests that the Examiner allow the application to proceed to grant therefore.

In the event that the Examiner has any questions or concerns regarding this Amendment, the Examiner is invited to contact the below-signed representative by telephone to discuss.

Respectfully submitted,

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Date

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